Targeting Treg-expressed STAT3 enhances NK-mediated surveillance of metastasis and improves therapeutic response in pancreatic adenocarcinoma

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Background

• PDAC has a low five-year survival rate of 9%.1
• PDAC is resistant to conventional and targeted therapies. Its immunosuppressive tumor microenvironment (TME) plays a large role.2

Methods

• For local orthotopic implantations mouse pancreata were injected with 200,000 KPC cells suspended in 50ul 10% RPMI followed by washout injection of 50μl PBS. Splenic vessels were then ligated with horizon clips and hemispleen was excised prior to closure. Splenic vessels were then ligated with horizon clips and 1 hemispleen was first ligated with horizon clips and 1 hemispleen was then excised prior to closure. 2. For metastatic orthotopic implantations spleens were injected with 200,000 KPC cells suspended in 50ul 10% RPMI followed by washout injection of 50μl PBS. Splenic vessels were then ligated with horizon clips and 1 hemispleen was excised prior to closure.

• Miniregional STAT3 ASO or control ASO were dosed 1 day prior to RT and maintained for the duration of treatment. RT treatment showed an over-expressed STAT3 signal within the NK and Treg immune cell subsets. STAT3 is known to be activated in PDAC; its expression correlates with tumor grade.3

• A lack of NK cells confers decreased survival in PDAC, while suppression of Tregs leads to increased survival. Dendritic cells are an important mediator, as STAT3 ASO therapy response is eliminated without DCs.4

• Stereotactic body radiation therapy (SBRT), used to treat PDAC, is resistant to conventional and targeted therapies. Immunosuppressive cells including Tregs are a core element of therapeutic resistance in pancreatic cancer, and response to RT is only enhanced when Tregs are depleted or the target of inhibition. Systemic delivery of a STAT3 anti-sense oligonucleotide (ASO) in combination with SBRT results in tumor growth regression, decreased metastasis, and reversal of immunosuppression.

• Tregs are a core element of therapeutic resistance in pancreatic cancer, and response to RT is only enhanced when Tregs are depleted or the target of inhibition.

• Targeting Treg-expressed STAT3 enhances NK-mediated surveillance of metastasis and improves therapeutic response in pancreatic adenocarcinoma. Conclusions

• Systemic delivery of a STAT3 anti-sense oligonucleotide (ASO) in combination with SBRT results in tumor growth regression, decreased metastasis, and reversal of immunosuppression.

• A lack of NK cells confers decreased survival in PDAC, while suppression of Tregs leads to increased survival. Dendritic cells are an important mediator, as STAT3 ASO therapy response is eliminated without DCs.

• Combination therapies such as STAT3 ASO with RT may improve response to treatment in pancreatic cancer.

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